

Introduction: Ciclosporin A (CsA) is considered to be a major component in the prophylaxis and treatment of acute and chronic graft-versus-host-disease (GvHD) after allogeneic hematopoietic stem cell transplantation (HSCT). However, impairment of renal function and CNS toxicity may complicate or even inhibit the use of calcineurin-inhibitors (CNI). Here, we report the use of sirolimus/MMF in two children with acute/chronic GvHD and significant CNI-associated toxicities. **Case Reports:** Two patients, a 14-year-old boy and a 4-year-old girl, were transplanted for ALL and AML, respectively. They received bone marrow from their HLA-identical siblings and GvHD-prophylaxis with MTX and CsA. Patient 1, the boy, stayed on CsA until day +27, when he complained of dizziness and disorientation. The cranial MRI findings were consistent with CsA-induced neurotoxicity. He was set on tacrolimus until day +95, when he presented with cerebral seizures and somnolence. In the absence of acute GvHD and the presumption of tacrolimus-induced neurotoxicity, the drug was discontinued. One week later, the presence of GvHD of skin and gut could be confirmed by biopsy. During his previous anti-leukemic therapy, the patient had suffered from severe side effects of high-dosed steroids. So, in an attempt to minimize the use of steroids, he was set on sirolimus/MMF with a short course of prednisone. He rapidly responded to this regimen. Steroids were discontinued after a few days. The boy stayed on sirolimus/MMF for four months without evidence of recurrent GvHD. Patient 2 was switched early to tacrolimus because of a status of stupor and suspected CsA-neurotoxicity. She developed stage 4 gut GvHD on day +45, responsive to a highly immunosuppressive therapy including infliximab. Eleven months post-transplant, while on tacrolimus, she had increasing renal insufficiency with a creatinine clearance of 30 ml/min and a urea of 120 mg/dl. She was set on sirolimus/MMF; in the transition phase to that regimen she had another, steroid-responsive flare of her gut GvHD. Eighteen months post-transplant, the girl's GvHD is under good control with sirolimus and low dose steroids. Renal function tests are within normal limits. **Conclusion:** In HSCT recipients with severe calcineurin-inhibitor neurotoxicity or impaired renal function, the use of sirolimus/MMF should be considered when continuation of immunosuppressive therapy is mandatory for control of GvHD.

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T CELLS OF RECIPIENT ORIGIN MEDiate THE DEVELOPMENT OF MURINE SYNGENEIC GRAFT-VERSUS-HOST DISEASE

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Syngeneic graft-versus-host disease (SGVHD), characterized by a T_H1 cytokine response, and intestinal inflammation develops following lethal irradiation, reconstitution with syngeneic bone marrow, and treatment for 21 days with cyclosporine A (CsA). It has generally been assumed that the T cell responses associated with SGVHD resulted from the reconstitution of irradiated recipients with donor bone marrow. However, to determine the origin of the effector cells that mediate SGVHD, syngeneic bone marrow from normal immunocompetent mice or immunodeficient mice were transferred into lethally irradiated recipients. Following CsA treatment, mice within both groups developed inflammation characteristic of SGVHD in the colon and liver. Furthermore, increases in the expression of T_H1 cytokines, levels of colonic $CD4^+$ T cells and expression of activated peripheral $CD4^+$ T cells were comparable regardless of whether CsA-treated animals received T cell sufficient (normal) or T cell deficient (SCID) bone marrow. These results demonstrate that in the absence of donor T cells, recipient T cells can expand and mediate the induction of CsA-induced SGVHD.

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FATAL TUMOR LYSIS SYNDROME ASSOCIATED WITH INDUCTION OF GRAFT-VS-HOST DISEASE IN A RELAPSED PATIENT WITH NASAL NK CELL LYMPHOMA AFTER TANDEM AUTOLOGOUS-ALLOGENEIC STEM CELL TRANSPLANTATION

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The effective therapy for nasal natural-killer (NK) cell lymphoma is not established, and there is no report that the graft-versus-lymphoma effect (GVLE) against the nasal NK cell lymphoma was definitively confirmed. We report a patient with nasal NK cell lymphoma who relapsed after allogeneic transplant and developed fatal tumor lysis reaction during the attempt of inducing graft-versus-host disease (GVHD). The patient was 53-year-old woman suffering from a rapidly progressing nasal NK cell lymphoma metastasis to the skin, adrenal gland and abdominal lymph nodes. She received three courses of combination chemotherapy followed by high-dose therapy with a rescue of autologous haematopoietic stem cell transplant (HSCT). Following attainment of partial remission, she underwent allogeneic HSCT from an HLA-matched sibling prepared with reduced-intensity regimen and attained complete remission. In the subsequent course, she had no acute GVHD, but had extensive chronic GVHD mainly on skin, requiring some immunosuppressions. Seven months after allogeneic HSCT, she developed fever and pancytopenia. A general search revealed bone marrow relapse without any other lesion. Immunosuppressions were tapered with expecting GVLE. Two weeks after the withdrawal, she suddenly developed tachypnea. Emergent laboratory data revealed significant hyperkalemia, hyperuricemia, metabolic acidosis. We also found the marked decrease of tumor cells in a bone marrow aspiration specimen. After the tumor lysis reaction, the patient developed severe renal and hepatic dysfunction, causing her death despite intensive care. This is the first case report that definitely confirmed a GVLE against NKCL.

HISTOCOMPATIBILITY/ALTERNATIVE STEM CELL SOURCES

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FACTORS PREDICT HEMATOPOIETIC RECOVERY IN PATIENTS WITH FANCONI ANEMIA (FA) AFTER ALTERNATE DONOR (AD) HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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As engraftment has been a significant barrier to successful AD HSCT (defined as bone marrow [BM] or umbilical cord blood [UCB] from a donor other than an HLA matched sibling), we attempted to identify risk factors predictive of hematopoietic recovery in this setting. Therefore, we evaluated engraftment in 83 FA patients aged 0.8–48.5 years (median 11.8) who underwent T cell depleted BMT [(TCD, n = 31), no TCD BMT (n = 37) or UCBT (n = 15)] at the University of Minnesota from 1990 to 2004. 55% had aplastic anemia and 34% had myelodysplastic syndrome/acute myeloid leukemia at time of HSCT; 34% were CMV seropositive; 60% had HLA matched donors. All received 40 mg/kg cyclophosphamide and 450 or 600 cGy total body irradiation with 65% also treated with fludarabine (FLU) 140 mg/m². BM Grafts contained $0.82\text{--}9.32 \times 10^6$ CD34 cells/kg and $0.66\text{--}2.57 \times 10^3$ CD3 cells/kg and UCB grafts contained $0.01\text{--}0.91 \times 10^6$ CD34 cells/kg and $0.03\text{--}0.24 \times 10^3$ CD3 cells/Kg. In univariate analysis, factors associated with significantly improved incidence of neutrophil recovery (>500/uL) were no TCD-BM (94%) and TCD-BM in presence of FLU (91%) compared to 83% and 68% in recipients of UCB